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Original Article

New First-line Immunotherapy-based Therapies for Unresectable Hepatocellular Carcinoma: A Living Network Meta-analysis

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Abstract

Background and Aims: Several first-line immune checkpoint inhibitor (ICI)-based combination therapies have been identified for unresectable hepatocellular carcinoma (uHCC). This network meta-analysis (NMA) aimed to provide the most updated evidence about the preferred first-line ICI-based regimens for uHCC. ***Methods:*** A comprehensive literature search was performed in various databases from database inception to May 2022. The phase 3 trials evaluating first-line single-agent ICIs, molecular-target agents (MTAs), or their combinations in uHCC were included. The main endpoints were overall survival (OS) and progression-free survival (PFS). Pooled effect estimates were calculated using a random effects model within the frequentist framework. Subgroup analyses based on etiology were also conducted. ***Results:*** Twelve trials at low risk of bias with 8,275 patients comparing 13 treatments were included. OS with atezolizumab plus bevacizumab was comparable to sintilimab plus IBI305 [hazard ratio (HR): 1.16; 95% confidence interval (CI): 0.80–1.68] and camrelizumab plus apatinib (HR: 1.06; 95% CI: 0.75–1.51). The combination therapies, apart from atezolizumab plus cabozantinib in OS and durvalumab plus tremelimumab in PFS, had higher P-score than single-agent MTAs or ICIs. The survival benefits were associated with a high risk of adverse events leading to treatment discontinuation. The proportion of patients with hepatitis B virus-related HCC receiving ICIs combinations might positively correlate with survival advantages (R^2=0.8039, p=0.0155). ***Conclusion:*** This NMA demonstrated that atezolizumab plus bevacizumab remains the stand of care and confers comparable survival benefits to sintilimab plus IBI305 and camrelizumab plus apatinib in first-line therapy for uHCC. The optimal treatment algorithms should consider efficacy, safety, and etiology.

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers and the leading cause of cancer-related mortality.[1] Systemic agents are the mainstay treatments in unresectable HCC (uHCC).[2] Sorafenib and lenvatinib, two kinds of tyrosine kinase inhibitors (TKIs), once served as the first-line regimens for uHCC with limited survival advantages for more than a decade.[3,4] Subsequently, some trials explore the efficacy of immune checkpoint inhibitors (ICIs) in this setting, and most failed to achieve primary endpoints.[5] Until 2020, the IMbrave150 trial demonstrated that the combination therapy of atezolizumab and bevacizumab was superior to sorafenib in survival benefits,[6] which dramatically changed the therapeutical landscape in uHCC.

At present, combination strategies of ICIs plus molecular-target agents (MTAs), including TKIs and monoclonal antibodies against vascular endothelial growth factor (VEGF), or dual ICIs have been reported in several randomized clinical trials (RCTs).[6–12] Recently, the outcomes of three phase 3 trials (LEAP-002,[11] SHR-1210-310,[10] and RATIONALE-301[9]) identifying first-line ICI-based treatments in uHCC were released. Almost of those treatments were designed to compare with the accepted standard (i.e. sorafenib, and lenvatinib). Due to the lack of head-to-head comparisons, these parallel trials have made the treatment landscape more complicated and yielded clinical questions regarding the selection of the optimal treatment.

Network meta-analysis (NMA) is an optimal technique to compare multiple therapeutic strategies across RCTs.[13] In recent years, several NMAs have been conducted to com-

Keywords: Hepatocellular carcinoma; Systemic therapy; Immunotherapy; Immune checkpoint inhibitors; Molecular targeted therapy; Tyrosine protein kinase inhibitors; Overall survival; Progression-free survival; Adverse effects; Network meta-analysis.

Abbreviations: CI, confidence interval; CTLA-4, cytotoxic T-lymphocyte-associated protein-4; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; ICI, immune checkpoint inhibitor; MTA, molecular-target agent; NMA, network meta-analysis; ORR, objective response rate; OS, overall survival; PD-(L)1, programmed death (ligand) 1; PFS, progression-free survival; RCT, randomized clinical trial; RR, relative risk; TRAE, treatment-related adverse event; VEGF, vascular endothelial growth factor; HCC, hepatocellular carcinoma; TKI, tyrosine kinase inhibitor; uHCC, unresectable hepatocellular carcinoma.

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pare these different treatment options for uHCC in the first-line setting.[14–17] However, the data of emerging studies and updates of previous trials were recently reported and may cause substantial changes in the results of those analyses.[9–11] Therefore, the present updated systemic review and NMA aimed to compare the efficacy and safety of various first-line therapeutic regimens in uHCC based on the latest available evidence.

Methods

Search strategy and selection criteria

This systematic review and NMA aimed to compare new first-line systemic therapies for uHCC. The reporting of this study was performed following the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement and was registered in PROSPERO (CRD42022323989).[18]

Phase 3 RCTs identifying first-line systemic treatments for uHCC were included. Interventions of interest included TKIs, ICIs, and ICI-based combinations. TKIs of interest included sorafenib, lenvatinib, and donafenib. Studies examining locoregional therapies alone or in conjunction with systemic medications in uHCC were excluded. The primary outcomes were overall survival (OS) and progression-free survival (PFS). Secondary outcomes were objective response rate (ORR), grade 3 or higher treatment-related adverse events (TRAEs), and TRAEs leading to treatment discontinuation. For multiple publications of the same trial or cohort, all reports were reviewed, and data from the most recent report were extracted.

A comprehensive electronic literature search was performed in PubMed, Web of Science, Embase, and Cochrane library from database inception up through May 2022. Before the final analysis, all databases were retrieved again for recent publications in early October 2022. The published language was limited to English. The detailed search strategy was reported in Supplementary File 1. An additional hand search of reference lists from included publications was also conducted. In addition, the relevant conference abstracts from major scientific societies in the field of oncology, including the American Society of Clinical Oncology and the European Society of Medical Oncology, were also retrieved. Two reviewers (JJC and ZCJ) independently identified eligible studies by reviewing full-text articles after initially screening the titles and abstracts from retrieved records. Disagreements were discussed and resolved by a third senior investigator (HDZ).

Data extraction

A structured data table with prespecified data elements, mainly including first author, year of publication, baseline characteristics, sample size, treatment scheme and outcomes, was designed to extract data from included studies. Two investigators (BL and RL) independently extracted data, and the discrepancies were resolved by referring to a third experienced investigator (HDZ).

Risk of bias

The Cochrane risk of bias assessment tool was used to evaluate the risk of bias, which consist of the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting.[19] Two independent investigators (ZCJ and YQW) independently evaluate the study quality. Disagreements were discussed and resolved by a third senior investigator (HDZ).

Statistical analysis

The statistical analysis was performed using R (version 4.1.1, R Project for Statistical Computing). When assessing OS and PFS, original hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) were directly abstracted from the included trials. When assessing ORR and TRAEs, the relative risks (RRs) and corresponding 95% CIs were calculated. Log-transformed treatment estimates with the corresponding standard error were calculated based on HRs or RRs with their 95% CIs. Mixed treatment comparisons were conducted using a random effect model within the frequentist framework.[20] League tables and forest plots were used to show indirect comparisons among different treatments after back-transforming the network estimates. P scores, which estimate the extent of certainty that a treatment is better than the competing treatments, were computed to rank treatments.[21] The rankograms were also created to portray treatments ranking based on P scores. Heterogeneity was assessed as Cochran's Q and I^2 statistics. Considering the possible impact of HCC etiology on therapeutic effects,[22] we conducted subgroup analyses for OS in HCC patients with hepatitis B virus (HBV), hepatitis C virus (HCV), and nonviral infection. Pearson or Spearman correlation analysis was performed to explore the correlation between HR for OS and proportion of HBV-related patients according to the normality of the data. The packages of "netmeta" (version 2.6-0) were used to perform NMA.

Results

Study characteristics

The literature search yielded 2,826 records. After the removal of duplicates, a total of 2,344 publications were evaluated by screening titles and abstracts, of which 67 met the eligibility for full-text review. 12 phase 3 trials were included in the systematic review and NMA (Fig. 1).[3–7,9–12,23–25] Two trials compared sorafenib with placebo.[3,23] Nine studies compared either TKIs (lenvatinib and donafenib),[4,24] programmed death (ligand)1 (PD-[L]1) (nivolumab and tislelizumab),[5,9] PD-(L)1 inhibitors plus TKIs or anti-VEGF monoclonal antibody (atezolizumab plus bevacizumab, sintilimab plus IBI305, atezolizumab plus cabozantinib and camrelizumab plus apatinib),[7,10,12,17] or durvalumab plus tremelimumab,[8] with sorafenib. One study compared pembrolizumab plus lenvatinib with single-agent lenvatinib.[11] All trials were powered to demonstrate superiority except for RATIONALE-301 (noninferiority and superiority),[9] Qin *et al*. (noninferiority and superiority),[24] and REFLECT (noninferiority).[4]

Two trials, COSMIC-32 and HIMALAYA, were three-arm designs.[8,12] The secondary endpoints included PFS for single-agent cabozantinib versus sorafenib, and OS for single-agent durvalumab versus sorafenib in these two trials, and the corresponding data were also considered in the present NMA. The data of the IMbrave150 trial used in this NMA were updated outcomes,[17] not those originally reported by Finn *et al*.[6] The study for the Chinese subpopulation of the IMbrave150 study was not included due to overlapped patients.[26] This NMA included a total of 8,275 patients, most of whom presented with Eastern Cooperative Oncology Group performance status of <2, and Child-Pugh class A liver function. The characteristics of the included studies are shown in Supplementary Table 1.

Risk of bias

The risk of bias was qualitatively evaluated using the Cochrane tool for risk of bias and was generally low across

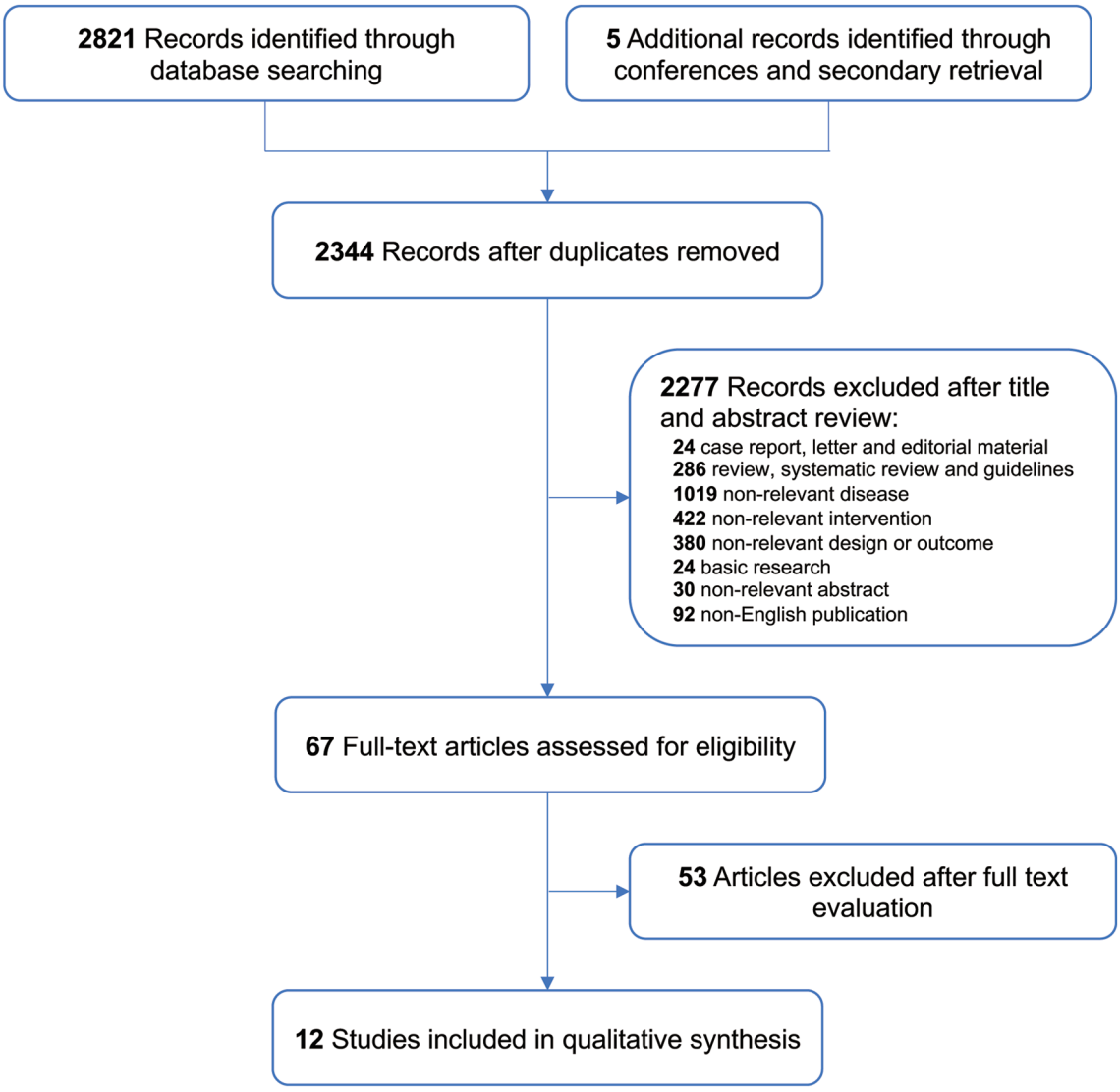

Fig. 1. PRISMA flowchart of screening and selection of studies.

all the included studies, which had low risk in at least five of seven domains (Supplementary Fig. 1). All trials, except for SHARP and Asia-Pacific, lacked blinding of participants and personnel. The independent radiologic review was implemented in all the trials apart from the HIMALAYA trial and *post hoc* assessment was conducted in the REFLECT trial.

OS comparison

All included 12 trials reported HRs for OS (Supplementary Fig. 2). The heterogeneity in OS evaluation was low with an overall I^2 statistics of 0% and a nonsignificant Cochran's Q test (Q=0.006, p=0.941). The results of NMA for OS were shown as a league table (Table 1). All the treatments showed OS benefits over the placebo. No significant differences in OS were observed among combination therapies except for atezolizumab plus cabozantinib.

Considering that atezolizumab plus bevacizumab has been recommended as the standard of care in the first-line setting, the comparisons between atezolizumab plus bevacizumab (exposure arm) and other treatments (comparators) were also conducted (Fig. 2A). Atezolizumab plus bevacizumab was significantly superior to lenvatinib (HR: 0.72; 95% CI: 0.54–0.96), sorafenib (HR: 0.66; 95% CI: 0.52–0.84) and placebo (HR: 0.45; 95% CI: 0.33–0.62), not significantly superior to the pembrolizumab plus lenvatinib (HR: 0.85; 95% CI: 0.61–1.19), durvalumab plus tremelimumab (HR: 0.85; 95% CI: 0.63–1.14), donafenib (HR: 0.79; 95% CI: 0.59–1.07), tislelizumab (HR: 0.78; 95% CI: 0.57–1.05), nivolumab (HR: 0.78; 95% CI: 0.57–1.05), durvalumab (HR: 0.77; 95% CI: 0.57–1.03), and atezolizumab plus cabozantinib (HR: 0.73; 95% CI: 0.51–1.06), and was comparable to sintilimab plus IBI305 (HR: 1.16; 95% CI: 0.80–1.68) and camrelizumab plus apatinib (HR: 1.06; 95% CI: 0.75–1.51). The combination therapies (except for atezolizumab plus cabozantinib) and donafenib were superior to sorafenib in terms of OS (Supplementary Fig. 3). As reflected by the P-score, sintilimab plus IBI305 ranked the highest in terms of OS (P-score=94.40%), followed by camrelizumab plus apatinib (P-score=89.12%) and atezolizumab plus bevacizumab (P-score=83.35%; Table 2 and Supplementary Fig. 4).

Table 1. League table for indirect comparisons among the first-line treatments for unresectable hepatocellular carcinoma

Treatment	Progression-free survival											
Overall Survival	*Sin +IBI305*	1.08 (0.79, 1.47)	0.86 (0.64–1.16)	1.02 (0.75, 1.38)	0.62 (0.48–0.81)	0.62 (0.47–0.81)	0.51 (0.39–0.67)	0.60 (0.46–0.79)	0.55 (0.42–0.71)	0.89 (0.58–1.35)	0.85 (0.66–1.10)	0.56 (0.45–0.69)
	0.92 (0.63–1.33)	*Cam +Apa*	0.80 (0.58–1.09)	0.94 (0.69–1.30)	0.58 (0.44–0.76)	0.57 (0.43–0.76)	0.47 (0.35–0.64)	0.56 (0.42–0.74)	0.51 (0.39–0.67)	0.83 (0.54–1.27)	0.79 (0.60–1.04)	0.52 (0.41–0.65)
	0.86 (0.60–1.25)	0.94 (0.66–1.33)	*Ate+Bev*	1.18 (0.87, 1.60)	0.72 (0.56–0.94)	0.72 (0.54–0.94)	0.59 (0.45–0.78)	0.70 (0.53–0.91)	0.64 (0.49–0.83)	1.03 (0.68, 1.57)	0.98 (0.76–1.28)	0.65 (0.53–0.80)
	0.74 (0.52–1.06)	0.80 (0.58–1.12)	0.85 (0.61–1.19)	*Pem+Len*	0.61 (0.47–0.80)	0.61 (0.46–0.80)	0.50 (0.38–0.67)	0.59 (0.45–0.78)	0.54 (0.41–0.70)	0.87 (0.57–1.34)	0.83 (0.71–0.98)	0.55 (0.44–0.68)
	0.73 (0.53–1.01)	0.79 (0.59–1.07)	0.85 (0.63–1.14)	0.99 (0.75–1.31)	*Dur+Tre*	0.99 (0.78–1.25)	0.82 (0.64–1.04)	0.97 (0.77–1.21)	0.88 (0.71–1.10)	1.43 (0.96, 2.12)	1.36 (1.10, 1.69)	0.90 (0.77–1.05)
	0.69 (0.49–0.95)	0.75 (0.55–1.01)	0.79 (0.59–1.07)	0.93 (0.70–1.24)	0.94 (0.74–1.19)	*Donafenib*	0.83 (0.64–1.07)	0.98 (0.77–1.24)	0.89 (0.71–1.12)	1.44 (0.96, 2.16)	1.38 (1.09, 1.73)	0.91 (0.76–1.08)
	0.67 (0.48–0.93)	0.73 (0.54–0.99)	0.78 (0.57–1.05)	0.91 (0.68–1.21)	0.92 (0.72–1.17)	0.98 (0.76–1.25)	*Tislelizumab*	1.18 (0.92; 1.52)	1.08 (0.85, 1.37)	1.75 (1.16; 2.62)	1.67 (1.31, 2.11)	1.10 (0.91, 1.32)
	0.67 (0.48–0.93)	0.73 (0.54–0.99)	0.78 (0.57–1.05)	0.91 (0.68–1.21)	0.92 (0.72–1.17)	0.98 (0.76–1.25)	1.00 (0.78–1.28)	*Nivolumab*	0.91 (0.73–1.14)	1.48 (0.99 2.20)	1.41 (1.13;1.76)	0.93 (0.79–1.10)
	0.66 (0.48–0.92)	0.72 (0.54–0.97)	0.77 (0.57–1.03)	0.90 (0.68–1.19)	0.91 (0.72–1.15)	0.97 (0.76–1.23)	0.99 (0.77–1.26)	0.99 (0.78–1.26)	*Durvalumab*	1.62 (1.09; 2.40)	1.55 (1.25;1.91)	1.02 (0.88; 1.19)
	0.63 (0.43–0.93)	0.69 (0.48–0.99)	0.73 (0.51–1.06)	0.86 (0.60–1.22)	0.87 (0.63–1.19)	0.92 (0.67–1.27)	0.94 (0.68–1.30)	0.94 (0.69–1.30)	0.96 (0.70–1.31)	*Ate +Cab*	0.95 (0.64;1.41)	0.63 (0.44; 0.91)
	0.62 (0.45–0.85)	0.67 (0.51–0.90)	0.72 (0.54–0.96)	0.84 (0.71–1.00)	0.85 (0.68–1.06)	0.90 (0.72–1.13)	0.92 (0.73–1.17)	0.92 (0.74–1.16)	0.93 (0.75–1.17)	0.98 (0.72–1.33)	*Lenvatinib*	0.66 (0.57; 0.77)
	0.57 (0.43–0.75)	0.62 (0.49–0.79)	0.66 (0.52–0.84)	0.77 (0.62–0.97)	0.78 (0.66–0.92)	0.83 (0.70–0.99)	0.85 (0.71–1.02)	0.85 (0.71–1.01)	0.86 (0.73–1.02)	0.90 (0.69–1.18)	0.92 (0.79–1.07)	*Sorafenib*
	0.39 (0.28–0.55)	0.43 (0.31–0.58)	0.45 (0.33–0.62)	0.53 (0.40–0.71)	0.54 (0.42–0.69)	0.57 (0.44–0.73)	0.58 (0.45–0.75)	0.58 (0.45–0.75)	0.59 (0.46–0.76)	0.62 (0.45–0.86)	0.63 (0.50–0.80)	0.69 (0.57–0.83)

Placebo

Hazard ratio (HR) and 95% confidence interval (CI) for pairwise comparisons of the network meta-analysis from indirect comparisons. The column treatment is compared with the row treatment. For overall survival, an HR of <1 favors column-defining treatment. For progression-free survival, an HR of <1 favors row-defining treatment. Ate+Bev, atezolizumab plus bevacizumab; Ate+Cab, atezolizumab plus cabozantinib; Cam+Apa, camrelizumab plus apatinib; Dur+Tre, durvalumab plus tremelimumab; Pem+Len, pembrolizumab plus lenvatinib; Sin+IBI305, sintilimab plus a bevacizumab biosimilar (IBI305).

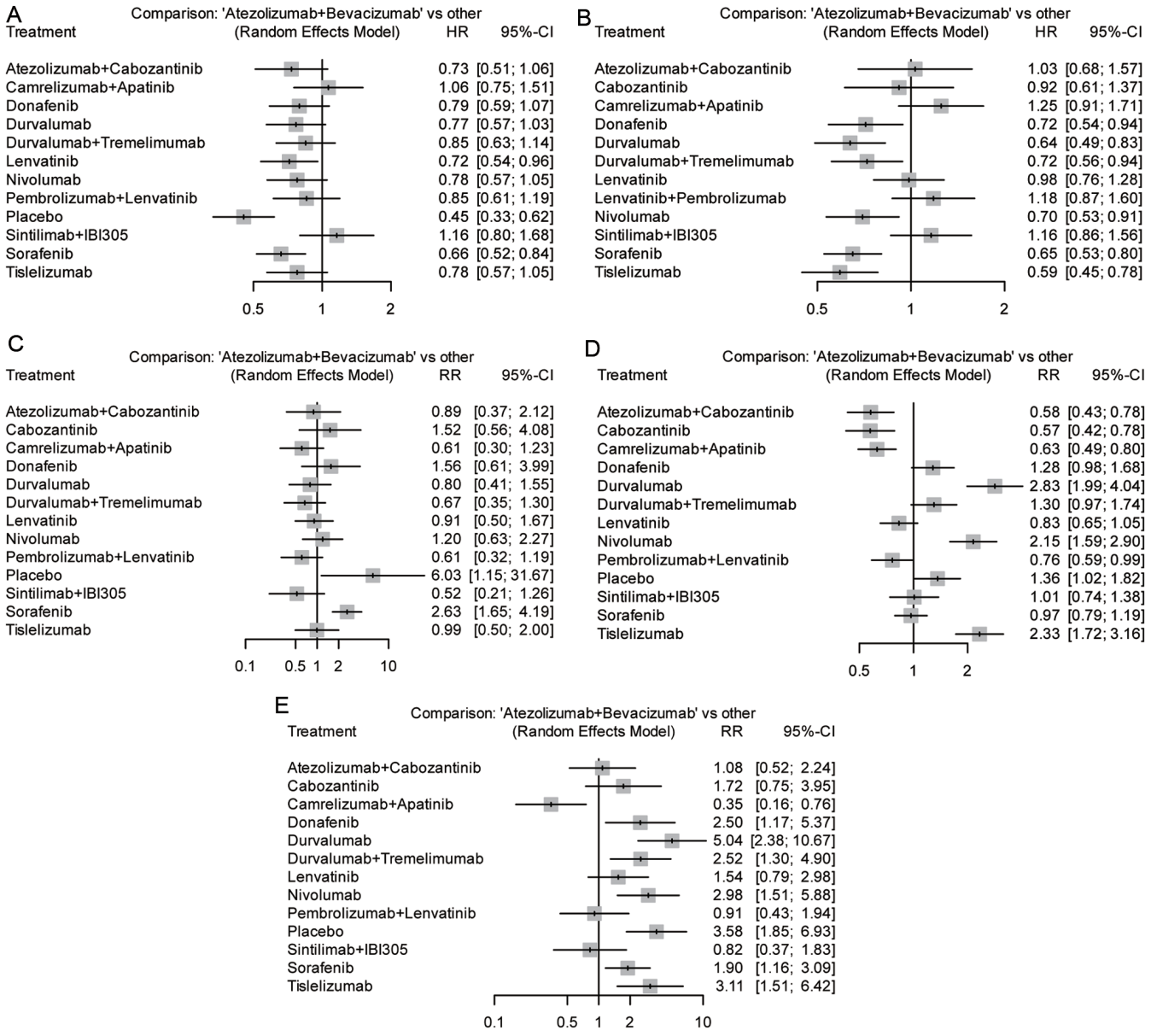

Fig. 2. Forest plots of efficacy. Overall survival (A), progression-free survival (B), overall response rate (C), Adverse events≥grade 3 (D), and leading to permanent discontinuation (E) considering atezolizumab plus bevacizumab as exposure and all other treatments as reference.

PFS comparison

Eleven of the 12 included trials reported HRs for PFS apart from two trials (SHARP and Asian-Pacific), which reported time to progression rather than PFS (Supplementary Fig. 5). The indirect comparisons among treatments for PFS are shown in Table 1. All treatments except for cabozantinib, durvalumab plus tremelimumab, donafenib, nivolumab, durvalumab, and tislelizumab were significantly superior to the sorafenib in PFS (Supplementary Fig. 6). There were no significant differences in terms of PFS among the combination therapies except for durvalumab plus tremelimumab, of which only pembrolizumab plus lenvatinib were significantly superior in PFS to lenvatinib.

We also compared atezolizumab plus bevacizumab with other treatments in PFS (Fig. 2B). Atezolizumab plus bevacizumab was superior to durvalumab plus tremelimumab (HR: 0.72; 95% CI: 0.56–0.94), donafenib (HR: 0.72; 95% CI: 0.54–0.94), nivolumab (HR: 0.70; 95% CI: 0.53–0.91), sorafenib (HR: 0.65; 95% CI: 0.53–0.80) and tislelizumab (HR: 0.59; 95% CI: 0.45–0.78), was comparable to camrelizumab plus apatinib (HR: 1.25; 95% CI: 0.91–1.71), pembrolizumab plus lenvatinib (HR: 1.18; 95% CI: 0.87–1.60), sintilimab plus IBI305 (HR: 1.16; 95% CI: 0.86–1.56), and atezolizumab plus cabozantinib (HR: 1.03; 95% CI: 0.68–1.57). Based on the P-score in PFS, camrelizumab plus apatinib was the highest ranked treatment (P-score=91.08%) followed by pembrolizumab plus lenvatinib (P-score=86.47%), sintilimab plus IBI305 (P-score=84.10%), atezolizumab plus cabozantinib (P-score=70.47%) and atezolizumab plus bevacizumab (P-score=66.84%; Table 2, Supplementary Fig. 7).

Table 2. Analysis of treatment ranking

Treatment	Overall survival		Progression-free survival		Objective response rate		Grade≥3 TRAE		TRAE leading to discontinuation	
	Rank	P-score	Rank	P-Score	Rank	P-score	Rank	P-score	Rank	P-score
Sintilimab plus IBI305	1	94.40%	3	84.10%	1	86.96%	7	47.67%	13	16.08%
Camrelizumab plus Apatinib	2	89.12%	1	91.08%	3	81.83%	12	11.66%	14	0.35%
Atezolizumab plus Bevacizumab	3	83.35%	5	66.84%	9	47.57%	8	47.00%	11	22.37%
Pembrolizumab plus Lenvatinib	4	63.05%	2	86.47%	2	83.09%	11	23.41%	12	18.57%
Durvalumab plus Tremelimumab	5	62.04%	8	33.59%	4	76.46%	5	67.86%	5	68.43%
Donafenib	6	49.57%	9	31.80%	12	26.32%	6	66.95%	6	67.75%
Tislelizumab	7	44.98%	13	5.44%	8	48.26%	2	91.09%	3	79.06%
Nivolumab	8	44.98%	10	28.62%	10	35.55%	3	87.47%	4	77.28%
Durvalumab	9	42.57%	12	13.92%	5	64.43%	1	98.34%	1	96.50%
Atezolizumab plus Cabozantinib	10	35.22%	4	70.47%	6	56.47%	13	6.13%	10	25.82%
Lenvatinib	11	28.24%	6	63.90%	7	53.61%	10	31.25%	9	41.99%
Sorafenib	12	12.47%	11	15.88%	13	8.18%	9	44.12%	7	51.90%
Cabozantinib	NA	NA	7	57.88%	11	28.17%	14	5.97%	8	47.90%
Placebo	13	0.02%	NA	NA	14	3.10%	4	71.06%	2	86.01%

ORR comparison

All included trials reported information on ORR assessed per RECIST 1.1 or RECIST criteria (SHARP and Asia-Pacific, Supplementary Fig. 8). All treatments except for the placebo had higher ORRs than sorafenib (Supplementary Fig. 9). Atezolizumab plus bevacizumab had a higher ORR than sorafenib (RR, 2.63; 95% CI: 1.65–4.19) and placebo (RR, 6.03; 95% CI: 1.15–31.67) without significant superiority to the remaining treatments (Fig. 2C). The sintilimab plus IBI305 ranked the highest in terms of ORR (P-score=87.0%), followed by pembrolizumab plus lenvatinib (P-score=83.1%), camrelizumab plus apatinib (P-score=81.9%) (Table 2, Supplementary Fig. 10).

TRAE comparison

The incidence of grade 3 or higher TRAEs and TRAEs leading to treatment discontinuation were compared in this NMA (Supplementary Figs. 11 and 14). The Asia-Pacific trial did not report the incidence of adverse events (AEs)≥grade 3. Three trials (IMbrave150, ORIENT-32, and Asia-Pacific) did not report the incidence of TRAEs leading to treatment discontinuation, which was approximately replaced by corresponding treatment-emergent adverse events.

When compared with sorafenib, durvalumab, tislelizumab, nivolumab, durvalumab plus tremelimumab, donafenib, and placebo showed lower grade 3 or higher TRAEs, atezolizumab plus bevacizumab and sintilimab plus IBI305 showed comparable TRAEs≥grade 3. The remaining treatments, especially atezolizumab plus cabozantinib, atezolizumab plus cabozantinib and cabozantinib, had much higher incidences of TRAEs≥grade 3 (Supplementary Fig. 12). Atezolizumab plus bevacizumab had a significantly lower risk of grade 3 or higher TRAEs than atezolizumab plus cabozantinib, cabozantinib, and camrelizumab plus apatinib, had a comparable risk than sintilimab plus IBI305 and sorafenib, and did an obviously higher risk than single-agent PD-(L)1 inhibitor (Fig. 2D). Three kinds of anti-PD-(L)1 agents ranked highest in reducing the risk of grade 3 or higher TRAEs, while PD-(L)1 inhibitors plus TKIs relatively ranked at the bottom (Table 2, Supplementary Fig. 13).

A similar trend was observed for TRAEs leading to treatment discontinuation (Fig. 2E, Supplementary Fig. 15). Atezolizumab plus bevacizumab conferred a significantly higher risk of TRAEs leading to treatment discontinuation than durvalumab, tislelizumab, nivolumab, durvalumab plus tremelimumab, donafenib and sorafenib, a comparable risk than sintilimab plus IBI305, pembrolizumab plus lenvatinib and atezolizumab plus cabozantinib, and significantly lower risk than camrelizumab plus apatinib (Fig. 2E). As reflected by P-score, the PD-(L)1 inhibitors alone and dual ICIs ranked at the top followed by TKIs and PD-(L)1 inhibitors plus MTAs (Table 2, Supplementary Fig. 16).

Joint evaluation for OS and TRAE

As shown in Figure 3, we also made graphical joint analyses between HRs for OS and RRs for TRAEs. Compared with sorafenib, sintilimab plus IBI305, camrelizumab plus apatinib, and atezolizumab plus bevacizumab achieved significant survival benefits, whereas camrelizumab plus apatinib seemed to obviously increase the risk of TRAEs≥grade 3 (Fig. 3A). Most ICIs plus MTAs had a good OS, but the incidence of TRAEs leading to treatment discontinuation was obviously increasing (Fig. 3B). The single-agent ICIs even dual ICIs combinations seemed to have better safety profiles with satisfactory efficacy than ICIs plus MTAs or TKIs.

Etiology analysis

The subgroup analyses based on disease etiology were conducted. All included trials reported the HRs for OS in patients with HBV, while three trials did not provide those in patients with HCV and noninfection/alcohol (Supplementary Figs. 17, 21, and 25).[7,23,24] As a forest plot based on etiology shown (Fig. 4), the clinical benefit varied according to the etiology of HCC and occurred more frequently in HBV-related HCC

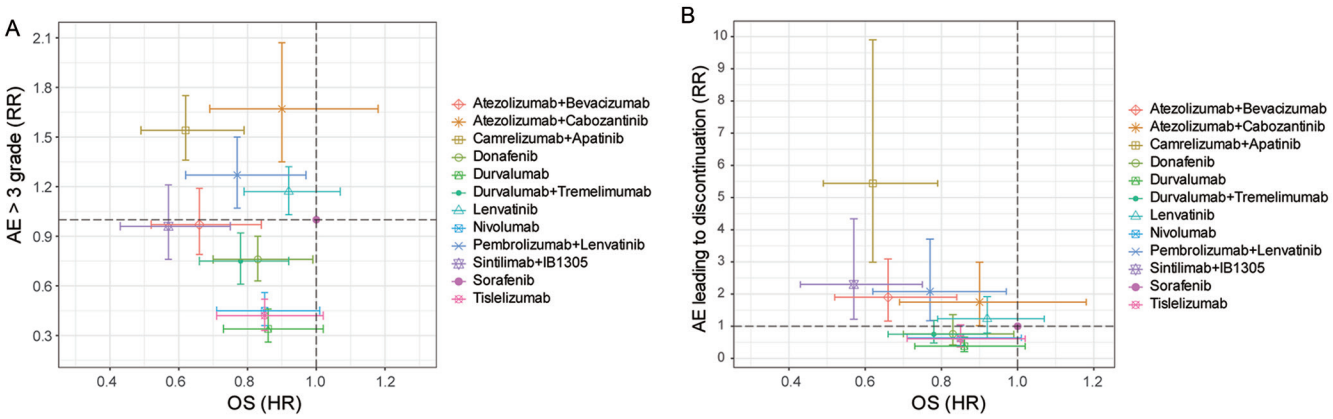

Fig. 3. Conjoint analysis of efficacy and safety. The relationship between hazard ratio (HR) for overall survival (OS) and relative risk (RR) for adverse events ≥grade 3 (A) or leading to treatment discontinuation (B), considering placebo as a reference, respectively.

patients with ICI-based therapies. Then we implemented correlation analysis of the impact of HBV for OS in patients treated with all treatments, ICI-based therapies, and ICIs combinations. There may be a negative relationship between the proportion of patients with HBV and HRs of OS based on study level (Fig. 5), which was more obvious in patients treated with ICIs combinations (R^2=0.8039, p=0.0155) than ICI-based therapies (R^2=0.6859, p=0.0058). The impact of HBV on survival benefits for patients treated with ICI-based therapies warrants to further exploration with rigorous statistical analysis.

For HCC patients with HBV, atezolizumab plus bevacizumab provided a numerical trend toward better OS than most of the treatments and conferred a similar survival benefit when compared to other combination therapies (Supplementary Fig. 18). When compared to sorafenib, almost all treatments were numerically better in OS, of which all combination therapies achieved significant survival advantages (Supplementary Fig. 19). According to P-score, all combination therapies were ranked higher than single-agent ICIs or MTAs (Supple-

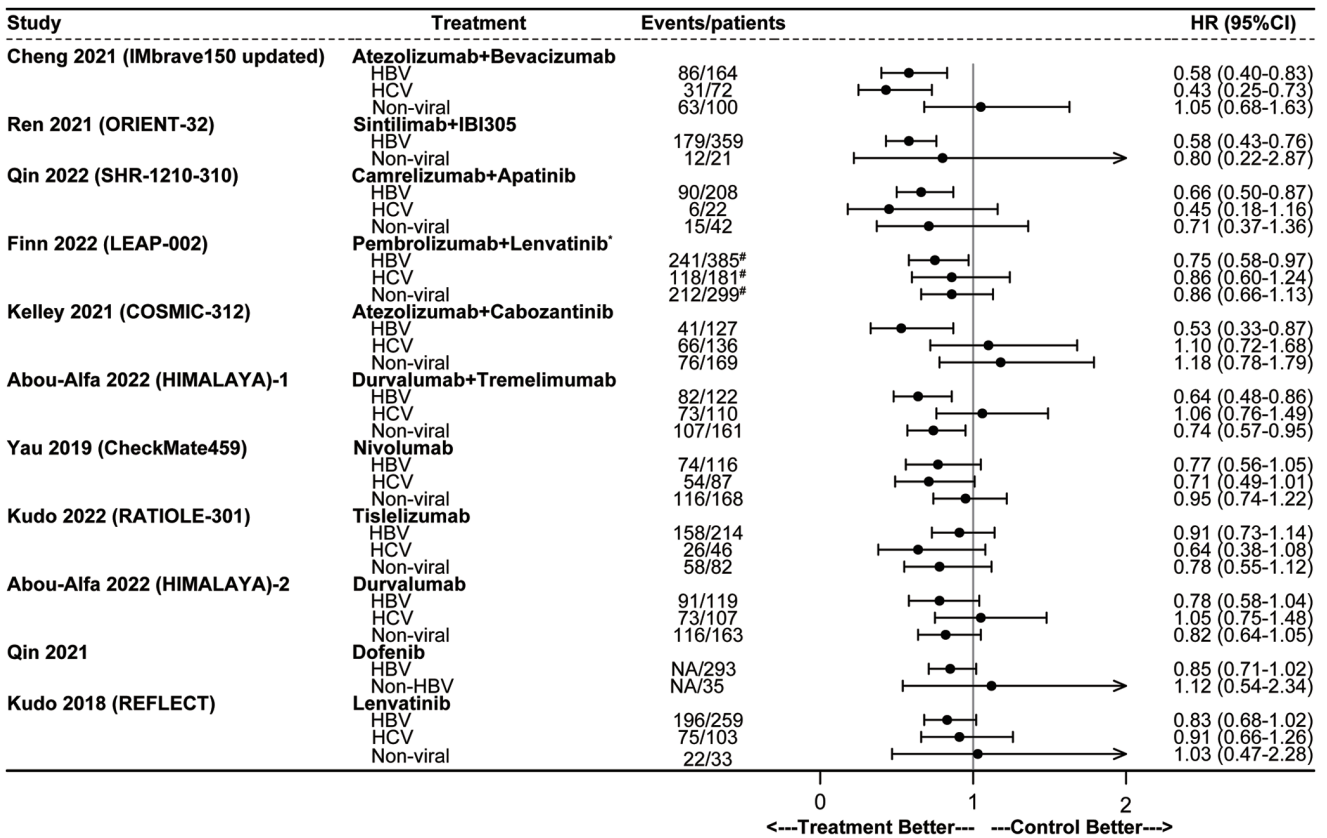

Fig. 4. Forest plots of overall survival based on etiology. *Control arm in Leap-002 was lenvatinib not sorafenib. #Number of events/patients were two arms of treatment and control, not single treatment arm due to lack of detailed data in Leap-002. HR, hazard ratio; HBV, hepatitis B virus; HCV, hepatitis C virus.

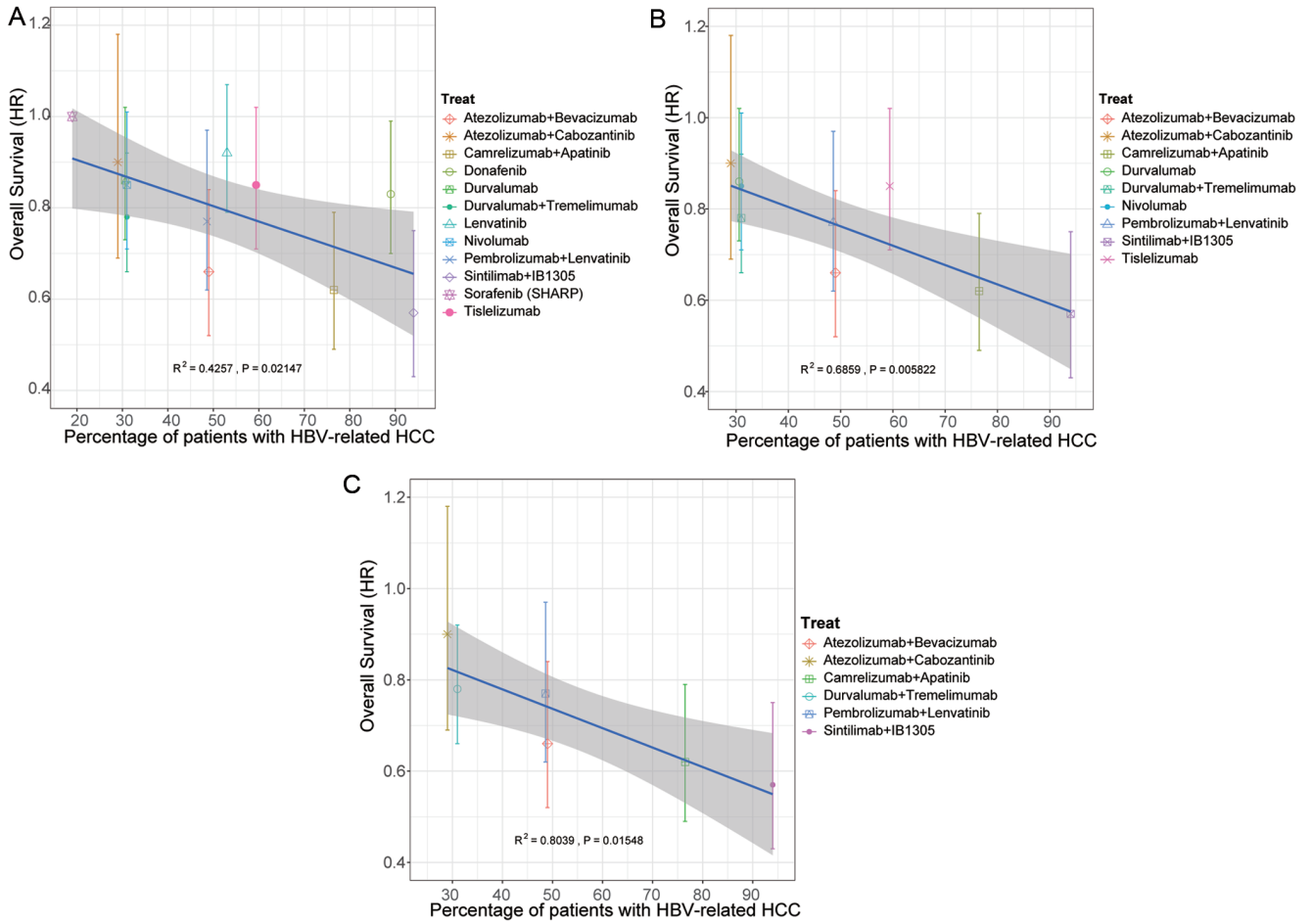

Fig. 5. Impact of hepatitis B virus on overall survival. Correlations between the hazard ratio of overall survival and the proportion of patients with hepatitis B virus-related hepatocellular carcinoma receiving all treatments (A), immune checkpoint inhibitors-based therapies (B), and immune checkpoint inhibitors combination therapies (C).

mentary Fig. 20). The results of subgroup analysis in patients with HCV-related HCC were reflected in Supplementary Figures 22–24. We found that atezolizumab plus bevacizumab had obviously numerical superiority over other treatments apart from camrelizumab plus apatinib with a similar survival advantage and significantly statistical superiority over durvalumab plus tremelimumab, durvalumab, lenvatinib and sorafenib (Supplementary Fig. 22). When compared with sorafenib, only atezolizumab plus bevacizumab provided survival benefit in patients with HCV infection (Supplementary Fig. 23). The corresponding results in patients with nonviral HCC were presented in Supplementary Figures 26–28. No significant differences in OS were observed between atezolizumab plus bevacizumab and the other treatments, or between the other treatments and sorafenib, in the subpopulation of nonviral hepatocellular carcinoma (HCC).

Discussion

In this systematic review and NMA, which included 12 randomized phase 3 clinical trials, we found that the PD-1/PD-L1 inhibitors-based combination therapies (with anti-VEGF or anti-cytotoxic T-lymphocyte-associated protein-4 [CTLA-4] or TKI) are now considered the first-line systemic therapies in patients with uHCC. There was similar clinical efficacy with comparable OS, PFS, and ORR among atezolizumab plus bevacizumab, sintilimab plus IBI305, and camrelizumab plus apatinib. When comparing the safety of different therapeutic regimens, we found single-agent PD-1/PD-L1 inhibitors (durvalumab, tislelizumab, nivolumab) were associated with lower proportions of TRAEs≥3 grade and permanent drug discontinuations. The results also indicated that dual checkpoint inhibition with durvalumab and tremelimumab has better tolerability than any other combination therapies, whereas the anti-PD-(L)1/ VEGF combinations reported lower risks of grades≥3 TRAEs than the combinations of anti-PD-1 plus TKI. We also found that ICI-based therapies potentially conferred survival advantages in patients with HBV-related HCC.

The success of the IMbrave150 study marked the transition toward ICI-based therapies for advanced HCC, and soon afterward the strategy of the combination of atezolizumab plus bevacizumab has quickly been recommended as the standard of care.[6,27] To date, there were four ICI-based combinations with different protocols (anti-PD-L1+anti-VEGF, anti-PD-1+anti-VEGF, anti-PD-L1+anti-CTLA-4, and anti-PD-1+TKI) that have been proven to be significantly superior to sorafenib.[6,7,28] The different antitumor mechanisms of these protocols may yield different efficacy and safety. For the PD-1/PD-L1 inhibitors, although both are monoclonal antibodies against the PD-L1/PD-1 axis, PD-1 inhibitors can also

block the binding of PD-1 to PD-L2 simultaneously.[29] A meta-analysis compared anti-PD-1 and anti-PD-L1, regarding efficacy and safety across various tumor types, and demonstrated that anti-PD-1 exhibited favorable survival outcomes and a safety profile comparable to that of anti-PD-L1.[30] CTLA-4 affects the priming and activation of lymphocytes early in the antitumor immune response, whereas PD-L1 modulates immune responses in the tumor microenvironment, downstream of lymphocyte activation.[29,31] There was a difference between monoclonal antibodies and kinase inhibitors in their modes of action at the target level.[32] Kinase inhibitors are less target-specific than monoclonal antibodies and could penetrate inside cells, further causing direct effects on cells, albeit with some risk of increased toxicity, whereas monoclonal antibodies have indirect effects and induce immune responses.[32,33]

These ICI-based therapeutic combinations have led to both successes and failures. The COSMIC-012 (atezolizumab plus cabozantinib) and LEAP-002 (pembrolizumab plus lenvatinib) trials have been reported with negative results.[11,12] The two combinations were associated with relatively longer PFS (rank second and fourth in terms of the P-score of PFS, irrespectively) among all protocols, but this did not translate into OS benefits. However, the PFS of durvalumab and tremelimumab were almost identical to sorafenib, ORR and OS were significantly higher.[28] This exposes the value of PFS as a surrogate for OS remains an unresolved Gordian knot, especially in patients treated with ICIs.[34] Thus, the major efficacy endpoint is OS for indirect comparisons in our study, despite there being some limitations in OS such as being influenced by follow-up duration, confounded by sequential therapies, and competing risk of death.[34,35] Other than the study endpoint, many study design factors can also affect the results of those trials, such as second-line treatment after progression, study population, selection of control arm, and so on.[35] Differing from most other studies, lenvatinib monotherapy was selected as the control arm in the LEAP-002 trial. Interestingly, based on indirect comparisons in our study, pembrolizumab plus lenvatinib could significantly improve the OS and PFS over sorafenib. This discrepancy highlights the complexity and dilemma of advanced HCC treatment strategies.

The etiology of underlying liver disease is an important concern that could influence the efficacy of ICIs therapy in HCC. The PD-1/PD-L1 axis is critical not only for cancer immune evasion but also for hepatitis virus infection.[36] Subgroup comparison analyses were also conducted in the HBV-related HCC patients. Anti-PD-(L)1 combination therapies show superiority over other monotherapies. The higher proportions of HBV-related HCC patients seem to be correlated with the better prognosis for different treatments in those studies. This trend was particularly evident in patients on ICIs therapy.

The incidence of high-grade toxicity and rates of withdrawal for each therapy were evaluated in this study. The results of ICI-based therapy in HCC patients were generally consistent with previous comprehensive studies for pan-cancer populations treated with ICIs.[37–39] The reported toxicity profile of anti-PD-(L)1 monotherapy presented lower incidences than anti-PD-(L)1 combination therapies.[37] Dual checkpoint inhibition was associated with a lower incidence of treatment-related adverse events (86.8% [80.9–91.1] for all-grade AEs; 35.9% [29.5–42.9] for grade 3 or higher AEs) across different combination therapies.[39]

The strengths of our study include the comprehensive spectrum of HCC systemic treatment, including recently disclosed data and analyses of not only survival but also response outcomes, safety, and etiology, whenever data were available. There are several limitations to this study. Based on the nature of NMA, most evidence stemmed from indirect comparison. This NMA was conducted with study level data instead of individual patient data. These may potentially influence the power of the analysis. In addition, several studies included in our NMA are still following up, and the efficacy data will be updated in the future. The updated NMA will be performed once new evidence or updated data emerges. Despite the above limitations, we believe that the results presented in our study are reliable and provide insight into the complex and changing therapeutic landscape of advanced HCC.

In conclusion, this study demonstrated that atezolizumab plus bevacizumab remains the stand of care and confers comparable survival benefits to sintilimab plus IBI305 and camrelizumab plus apatinib. The survival benefits were associated with the high risk of adverse events leading to treatment discontinuation. Patients with HBV-related HCC seemed to benefit more from ICI-based therapies in OS. The optimal treatment algorithms should consider efficacy, safety, and etiology.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Had full access to all of the study data and take responsibility for the integrity of the data and the accuracy of the data analysis (JJC, GJT), contributed equally (JJC, ZCJ), designed the protocol for the systematic review (JJC, GJT, HDZ), assessed the availability of each study retrieved from online databases (JJC, ZCJ), extracted and validated data (BL, RL), assessed the risk of bias (ZCJ, YQW), conducted statistical analysis and interpretation of data (JJC, RL, YQW), drafted the manuscript (JJC, ZCJ), and made critical revisions of the manuscript for important intellectual content (GJT, HDZ).

Data sharing statement

No additional data are available.

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